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REVIEW ARTICLE

Pharmacological and surgical treatment of patent ductus arteriosus in preterm newborns: an integrative review

Tratamento medicamentoso e cirúrgico para persistência do canal arterial em recém-nascidos pré-termos: uma revisão integrativa

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ABSTRACT

Introduction: Patent ductus arteriosus (PDA) is a very common complication among preterm newborns (NB), can cause serious complications and there are several types of treatment for this occurrence, being them pharmacological or surgical. **Objective:** To review the existing literature regarding the treatment of patent ductus arteriosus in preterm newborn (PTNB). **Methods:** This is an integrative review that used articles published in the PubMed, Scopus and Web of Science databases during the period of March and April 2023. The descriptors used were: "patent ductus arteriosus" and "treatment". Inclusion criteria were used: language of the article was written (English), type of article (clinical trials) and time of publication (last 5 years). From the search, 13 papers were identified. Results: Among the included articles, 84.61% did considered phamacological treatment for PDA and 15.39% specifically evaluated the surgical methods. Of the drugs proposed for the treatment of PDA, seven (53.8%) used ibuprofen, six (46.4%) paracetamol, two (15.6%) indomethacin, and two (15.6%) paracetamol and ibuprofen. Arterial closure occurred in 53.64% of the cases, no occlusion in 45.26% and death in 1.08% the children died. **Conclusions:** There is no consensus on the optimal treatment for PDA, although surgical interventions, which are considered only as a last option, there is a trend toward greater demand for transcatheter surgery and a general decline in studies with traditional surgical treatment.

Keywords: Infant; Premature; Congenital Abnormalities; Heart Defects, Congenital; Ductus Arteriosus.

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RESUMO

Introdução: A persistência do canal arterial (PCA) é uma complicação muito comum entre recém-nascidos (RN) pré-termos, pode gerar complicações graves e há vários tipos de tratamento para essa intercorrência, sendo eles medicamentoso ou cirúrgico. **Objetivo:** revisar a literatura existente a respeito do tratamento persistência do canal arterial em recém-nascidos pré-termos (RNPTs). **Métodos:** Trata-se de uma revisão integrativa, que utilizou artigos publicados nas bases de dados PubMed, Scopus e Web of Science, durante o período de março e abril de 2023. Os descritores utilizados foram: "persistência do canal arterial" e "tratamento". Foram utilizados como critérios de inclusão: o idioma em que o artigo foi escrito (inglês), tipos de artigo (ensaios clínicos) e tempo de publicação (últimos 5 anos). A partir da busca, foram identificados 13 trabalhos. **Resultados:** Dos estudos, 84,61% discorreram a respeito do tratamento medicamentoso para PCA e 15,38% avaliaram, especificamente, os métodos cirúrgicos. Dos medicamentos propostos para tratamento de PCA, sete (53,8%) usaram ibuprofeno, seis (46,4%) paracetamol, dois (15,6%) indometacina e dois (15,6%) paracetamol e ibuprofeno. Em 53,64% dos casos, houve fechamento do canal arterial, 45,26% não houve fechamento e em 1,08% as crianças morreram. **Conclusão:** Não há um consenso a respeito do tratamento ideal para PCA, embora dentre as intervenções cirúrgicas, que são consideradas apenas como última opção, existe uma tendência de maior procura pela cirurgia transcateter e uma queda, de forma geral, pela busca do tratamento cirúrgico tradicional.

Palavras-chave: Criança; Prematuro; Anomalias congênitas; Defeitos cardíacos congênitos; Canal arterial

Introduction

A pregnancy usually lasts around 40 weeks but can vary between 37 and 41 weeks. Newborns after this time are considered post-term, while preterm newborns are those born before 37 weeks of gestation. These cases should be followed and may have some complications[1]. There are risk factors associated with the birth of preterm newborn (PTNB), such as being twins or having previously given birth prematurely. Common complications due to prematurity include Patent Ductus Arteriosus (PDA)[1].

PDA is an arterial communication between the atrial chambers (1.5 mm), important structures for the proper functioning of the fetal circulation, which does not close after the birth of the baby, which can cause complications such as heart failure and increase in pulmonary pressure[2]. It can also occur in combination with other congenital infections[3]. The closure mechanism involves interactions between smooth muscle cells, endothelial cells, and the extracellular matrix (ECM). The ECM plays a role in this because it contains elastin, collagen, proteoglycans, hyaluronic acid and non-collagen glycoproteins that develop, maintain and repair the cardiovascular system[4].

Currently, there are three types of treatments for PCA, namely conservative, pharmacological, and surgical[5]. Among the pharmacological treatments, intravenous indomethacin and ibuprofen are the first choice to close the ductus arteriosus. These substances decrease the levels of prostaglandins, which promote the constriction of the muscular wall of the arterial duct, leading to fibrosis. However, there are adverse effects associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as impaired renal function, gastrointestinal bleeding, necrotizing enterocolitis, intestinal perforation, thrombocytopenia, pulmonary hypertension, and hyperbilirubinemia[6]. The administration of paracetamol has been associated with success in closing the ductus arteriosus in preterm infants, because it is an inhibitor of prostaglandin synthesis and has a better safety profile than indomethacin and ibuprofen, with a low rate of adverse effects and no detrimental effect on cerebral oxygenation[6,7].

Adequate management of PDA in preterm infants is essential for rapid closure and to avoid complications

associated with the use of NSAIDs. Published randomized clinical trials have not reached a consensus on the management of PDA, especially in preterm newborn (RNPTs), who often present acute respiratory distress and other complications. The diagnosis is usually made by auscultation of a systolic murmur and confirmed by cardiac echocardiography (echocardiography). In Brazil, the treatment is directed according to therapeutic conditions established in the hospital routine. Taking this into account, this study aimed to review the existing literature on the treatment of PDA in PTNBs.

Methods

Search strategy

An integrative review was conducted using the Patient, Intervention, Comparison and Outcome (PICO) strategy with the guiding question: "What are the indicated treatments (conservative, pharmacological and surgical) for patent ductus arteriosus in PTNBs?" The databases used were PubMed, Scopus and Web of Science, reviewing the studies title and abstract to identify those related to the topic. Searches were conducted between March and April 2023. The following descriptors were included in the search strategy: patent ductus arteriosus AND treatment. Only English language, originals articles, human studies published in the last five years were included in the review. All researchers independently reviewed the title and abstract to identify the eligible studies, and, if there was any doubt about the inclusion of the article, discussion among the authors took place to reach a consensus.

Criteria for data inclusion and exclusion

Inclusion criteria were type of experimental design (randomized controlled clinical trials and no control group studies), type of intervention (conservative, pharmacological or surgical), published in English in the last five years. Studies with RNs >36 weeks, no parameters to detect PDA and review studies were excluded. After applying the criteria, the studies were read in full. The data were extracted into a standardized spreadsheet containing information about the author, year, research goal, sample "n", PTNBs gestational age, pre- and post-treatment outcomes and their units of measurement (mm/kg, PDA diameter, number of days and, in some studies, the presence and closure information). As shown in Figure 1, the search yielded 57 studies, of which 37 were excluded after reading the title/abstract. After the full reading, seven were excluded and thirteen remained for the review.

Assessment of the quality of studies

The quality of studies was measured using the Dows and Black Tool (Figure 2), a scale recommended by the Cochrane Collaboration for experimental studies, which encompasses 27 questions that assess quality in the areas of reporting (information needed), external validity, selection bias and measurement and power of findings. Each question has a value of one point, and some have a value of two points (reporting domain). The studies were analyzed by all the researchers. The cut-off point for integrative review was categorized with a score of less than 14 points (low quality) and equal to or greater than 14 points (high quality).

Results

Of the 57 articles identified, 20 were selected and seven were excluded (Figure 1). Thirteen articles remained for review, of which 84.6% presented pharmacological methods to treat PDA and, as a last option, surgical procedures (surgical ligation or transcatheter) were performed if the drugs did not work (Table 1). The diameter of the PDA considered for diagnosis was >1.5mm. The parameters used to evaluate the PDA were: diameter of the channel in 61.5%, the diameter measurement in mm/kg in 7.8%, and the days to occlusion in 30.9% (cardiac auscultation). The studies that used surgical treatment aimed to determine which parameters could be used to predict the best treatment (pharmacological, surgical, or natural occlusion) or to analyze the trend for surgical ligation or transcatheter closure of the PDA.

Of the drugs proposed for the treatment of PDA, seven (53.8%) used ibuprofen, six (46.4%) used paracetamol, two (15.6%) used indomethacin, and two (15.6%) paracetamol and ibuprofen. Thirteen studies were analyzed, of which four (30.8%) presented a conservative treatment or control group. Articles compared different treatment combinations to close PDA, considering different drugs (indomethacin, ibuprofen, paracetamol), patient characteristics, time to start treatment after birth, route of administration and adverse effects.

Discussion

Pharmacological treatment

Regarding pharmacological treatment, ibuprofen was used in the studies because it was effective in closing the DA and was the shortest treatment; however, it had the most adverse effects. Additionally, according to Olsson et al. (2019)[12], the researchers stated that only 35% of patients who used ibuprofen had positive results in the PDA. Adverse effects observed include impaired renal and hepatic function, gastrointestinal bleeding, arterial hypertension and increased hyperbilirubinemia[6,7].

Based on specific characteristics of NBs and their influence on ibuprofen treatment, it was observed that lower gestational age (GA) and weight to GA increase the efficacy of ibuprofen. Additionally, early treatment initiation ensures greater effectiveness in outcomes[16].

There were differences in the route of administration. According to Lu et al. (2019)[14], the best route of treatment would be oral, because it is less expensive and safer than intravenous therapy. However, the rectal route was more

Table 1. Description of studies inserted in review (n=13).

Author (Year)	Objective	Sample "n"	GA (weeks)	Treatment	Pre-treat	Post-treat
Liu et al. (2022)[9]	To predict which treatment would be best for each PDA	n=42 G1: 15 G2: 27	≤30	G1: NSAID or surgical bandage G2: spontaneous closure	Intervention group: Size/weight PDA (mm/kg) Echocardiogram G1: 12h – 2,6 (0,7) 24h – 3,1 (0,8) 48h – 3,4 (0,9) 72h – 3,6 (3,2–3,8) G2: 12h – 2,1 (0,7) 24h – 1,8 (0,9) 48h – 1,6 (1,1) 72h – 1,5 (0– 2,1)	Deaths G1: 3 (20,0%) G2: 2 (7,4%)
O' Byrne et al. (2020)[5]	To evaluate PDA treatment preference by CT-PDA or O-PDA	n=6214 G1: 5919 G2: 295	24 - 27	G1: surgical bandage G2: Transcatheter	Age closure of PDA (days) Presence of PDA by auscultation G1: 23 (14-34) G2: 74 (44-105)	ADC
Potsiurko et al. (2021)[10]	To evaluate the relationship between PDA, serum NT-pro BNP levels at 2-3 and 8-9 days of life and BPD/deaths in very young infants premature infants	n=52 G1: 25 (PBD/ deaths) G2: 27 (Without PBD)	<32	G1: Paracetamol ou Ibuprofen G2: Control	Diameter PDA>1,5mm Echocardiogram	G1: 8/25 ADC 7/25 deaths by other causes G2: 11/27 ADC
Pan et al. (2023)[11]	To explore the efficacy and safety of the dexibuprofen suppository in the treatment of PDA in premature infants	n=87 G1: 44 G2: 43	< 34	G1: Oral ibuprofen G2: ibuprofen suppository	Presence of PDA by auscultation	G1: 1ª dose - 23/44 FCA 2ª dose - 9/44 FCA surgical - 4/44 FCA spontaneous - 8/44 FCA G2: 1ª dose - 25/43 FCA 2ª dose - 11/43 FCA surgical - 2/43 FCA spontaneous - 5/43 FCA
Olsson et al. (2019)[12]	To evaluate possible associations between protein marker serum and PDA result	n=47 G1: 25	22 – 27	Ibuprofen	PDA Diameter > 1,5mm Echocardiogram	G1: 7/25 ADC at 24h 13/25 no ADC 6/25 ADC (spontaneous late) 5/25 excluded

Liebowitz et al. (2019)[13]	To evaluate the efficacy of drugs used to treat PDA in newborns <28 weeks	n=202 G1: 98 G2: 27 G3: 38 G4: 39	28	G1: Conservative G2: Acetaminophen G3: Ibuprofen (or associated with acetaminophen) G4: Indomethacin	PDA Diameter > 1,5mm	G1: 20/98 ADC 43/98 treats (6/15 ADC acetaminophen; 5/15 FCA ibuprofen + acetaminofeno; 8/13 indomethacin) 35/98 excluded G2: 7/26 ADC (1 deaths) G3: 15/35 FCA (3 deaths) G4: 23/27 FCA (2 deaths)
Bahrami et al. (2021)[6]	To evaluate the efficacy and adverse effects in administering high doses of paracetamol to close PDA	n=46	< 37	Paracetamol	PDA Diameter > 2,5mm Echocardiogram	8/46 no ADC 38/46 ADC
Dani et al. (2021)[7]	To check the effectiveness of intravenous paracetamol administration and learn about side effects for PDA treatment.	n=101 G1: 52 G2: 49	25 - 31	G1: Paracetamol G2: Ibuprofen	PDA Diameter>1,5 mm Echocardiogram	G1: 1st dose: 27/52 ADC 2nd dose (I) = 4/10 ADC G2: 1st dose: 38/49 ADC 2nd dose (I) = 2/4 ADC
Lu et al. (2019)[14]	To evaluate the efficacy of oral ibuprofen and paracetamol in the treatment of PDA in NB GA < 30 with or without < 1500g	n=255 G1: 83 G2: 85 G3: 87	<30	G1: Standard ibuprofen G2: Ibuprofen high dose G3: paracetamol	Presence of PDA by auscultation	G1: 53/83 ADC G2: 61/85 ADC G3: 33/87 F ADC
Oboodi et al. (2020)[15]	To determine whether the combination of paracetamol with ibuprofen is more effective than the individual use of these drugs to treat PDA.	n=154 G1: 67 G2: 68 G3: 19	<34	G1: Acetaminophen G2: Ibuprofen G3: Acetaminophen + Ibuprofen	Diameter PDA ≥1,5 mm Echocardiogram	G1:1st dose 51/67 ADC 2nd dose 7/67 ADC G2: 1st dose 52/68 ADC 2nd dose 10/68 ADC G3: 1st dose 15/19 ADC 2nd dose 4/19 ADC

Engbers et al. (2022)[16]	To quantify the contribution of patient characteristics and exposure to ibuprofen to the closure of PDA.	n=263	23,7-30	Ibuprofen	Mediana - 2,2 (1,2-4,1) mm	55/263 ADC after three doses (first week of life) n = 208 Treat < 8d - 52/128 ADC Treat > 8d -3/80 ADC
Mydam et al. (2019)[17]	To recognize clinical identifiers related to acid-base status that could predict PDA indomethacin-induced closure	n=91	<28	Indomethacin	PDA Diameter > 1.5mm	62/91 ADC 29/91 no ADC
Aikio et al. (2021)[18]	To evaluate the association between acetaminophen treatment and inflammatory biomarkers.	n=56 G1: 23 G2: 08 G3: 25	<32	G1: Paracetamol preparas G2: Paracetamol open study G3: control	Presence of PDA by auscultation	Closure: n (hours) G1: 177 (338) G2: 590 (238) G3: 336 (517)

Legend: G: group; ADC: atrial ductus closure; NSAIDs: non-hormonal anti-inflammatory drugs; GA: gestational age; PDA: persistent ductus arteriosus: DA: ductus arteriosus. Source: Authors (2023).

indicated in PTNBs with intestinal dysfunction, due to a lower number of adverse effects in the gastrointestinal tract compared to the oral route, even though the same efficacy was demonstrated in both forms of drug administration[11].

One study comparing treatment with ibuprofen and indomethacin, and indomethacin, it was found that both reduce prostaglandin levels and have the to promote constriction of the DA muscle wall[6]. When assessing efficacy, the use of indomethacin was more effective than ibuprofen in closing DA; the treatment with it was initiated because ibuprofen did not produce results within 48 hours[13]. In contrast, the study by Engbers et al. (2022)[16] showed that treatment with indomethacin was less effective compared to the ibuprofen treatment.

When Indomethacin was used, the clinical signs had to be monitored at the bedside to accurately assess the newborn's response to treatment. Increases in excess bases and hematocrit are predictors of treatment success in newborns, as indomethacin is not very effective in acids environments because acidosis favors dilatory forces[17].

Another drug that has been studied was paracetamol, which shown to be effective in reducing the concentration of inflammatory interleukins, leading to DA closure[18]. The use of high doses of paracetamol, indicating efficacy for occluding DA, did not result in liver changes, bleeding tendencies, and/or gastrointestinal disorders[6]. On the other hand, there is evidence that paracetamol has adverse effects such as renal and hepatic insufficiency and intestinal perforation in small numbers[7]. Liebowitz et al. (2019)[13] confirmed that paracetamol is not effective and suggested to replace it with indomethacin if there is no beneficial effects within 48h.

Surgical treatment

All analyzed articles consider conservative or pharmacological treatment before proposing surgical procedure. Surgical technique for the DA ligament consists of positioning the patient, already anesthetized, on the operating table in the right lateral decubitus in the direction of the ventral decubitus, with the left arm stretched over the head. Depending on the size of the child, an incision is made along the inferior edge of the scapula, through which the DA is dissected and sutured twice with polyester 2/0 wires and a polypropylene 4/0 transfixing tip[19] (Santos et al., 1992).

DA ligation is the traditional surgical method to resolve PDA; although effective, it has been associated with relevant adverse effects of general anesthesia after ligation, such as: bone marrow paralysis, pneumothorax, and transient myocardial dysfunction[20]. In addition, significant left ventricular (LV) systolic dysfunction was demonstrated on the first day after the surgical ligation, which may have as predictors the size of the PDA and the age of the child[21]. Moreover, with abrupt closure, the increase in LV distensibility must be greater to receive the blood volume and consequently the greater force generation that was previously reduced due to communication between the atria.

An alternative method is the transcatheter closure of the PDA, which was previously limited to older infants, and has been observed in hospitals since 2017[5]. Catheter closure is

performed under general anesthesia. A femoral vein puncture is performed, and then a flexible guidewire JR or vertebral curve catheter is inserted and positioned through the right ventricle and DA. The procedures is guided by transthoracic echocardiography and fluoroscopy. A device is implanted through the catheter at the DA to promote its closure[22].

O'Byrne et al. (2019)[5] reviewed the utilization of ligation and transcatheter treatment and found a general decrease in mechanical PDA intervention and a significant increase in the demand for transcatheter closure. The possible reason is the procedure association with cases where the intervention occurred in later postnatal age[5]. The reasons for the increase in the use of transcatheter closure could not be determined, but the limitations and lack of uniformity in the results of both pharmacological treatment and traditional surgical ligation are significant drawbacks, especially when added to the increased risk of adverse effects with no apparent additional benefit of these treatments.

The parameter used to predict the surgical intervention or not is the ductus measure, defined by echocardiography[9], and symptoms of PDA and newborn weight over a predetermined interval of hours are also considered[20]. Ductus diameter is also associated with blood pressure waves[23]. Thus, the pressure may be a marker for diagnosis and routine monitoring of PDA[24].

This review has some limitations. Blinding, randomization, and lack of power were limitations found in the studies. Statistical analysis of these data by meta-analysis would provide accurate estimates of the effects of the treatments, the dosage to be used, and the time required to close the ductus arteriosus. Strengths of the present study were the need for guidelines for the treatment of PDA, as well as the establishment of a first standard protocol and alternatives since several drugs are available. However, it seems that in all the studies there is a consistency in the cut-off point of the diameter of the duct (>1.5mm) to consider it persistent and start the intervention.

Conclusion

In conclusion, the articles reviewed indicate that there is no consensus about the treatment for PDA, however, overall, surgical intervention is considered only when conventional and pharmacological treatment fail. Also, among the drugs used, paracetamol is less effective and there is no recommendation for its use as standard treatment. Indomethacin and ibuprofen are the most indicated, but DA closure with indomethacin is dependent on RNPT weight. Ibuprofen appears to have the least effect on cerebral and mesenteric blood flow which minimizes adverse effects.

Author's Contributions

We describe contributions to the papers using the taxonomy (CRediT) provide above: *Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing*: GV; LFA; MESG; JVMS; MB; LSP; VS. *Project administration, Supervision & Writing – original draft: VS. Validation & Software: -. Resources & Funding acquisition: -. Data curation & Formal Analysis*: VS.

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